REMARKS

A check for $1010 for the fee for a three-month extension of time ($510) and the fee for four additional independent claims and four additional dependent claims ($500) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1, 3-8, 10-12, 14-32, 34-35 and 37-41 are currently pending in this application. Claims 1, 12, 14, 15, 17-20 and 34-35 are amended herein. Claim 36 is cancelled herein without prejudice or disclaimer. New claims 37-41 are added.

Claim 1 is amended to specify that the weight ratio of the one, or more than one hydrodynamic fluid-imbibing polymer to the one, or more than one hydrostatic pressure modulating agent is from about 35:1 to about 167:1, and the weight ratio of the one, or more than one hydrodynamic fluid-imbibing polymer to the agent of interest is from about 1:1 to about 9:1. Support for the recited ranges of weight ratios is provided in Tables 1-7 of Examples 2-8. The following table lists the amount of the hydrodynamic fluid-imbibing polymer(s) (A), the amount of the hydrostatic pressure modulating agent (B), and the amount of the active agent (C) constituents listed in Examples 2-8, as well as the values of A/B and A/C, which have been calculated from the listed amounts of A, B and C in each example.

	Example Number						
Component (mg)	2	3	4	5	6	7	8
Hydrodynamic fluid-imbibing polymer(s) (A)	Carbopol® 971P (280 mg)	Carbopol® 971P (320 mg)	Carbopol® 971P and Carbopol® 934P (total = 180 mg)	Carbopol® 971P (171 mg)	Carbopol® 971P (171 mg)	Carbopol® 971P (203.7 mg)	Carbopol® 971P (200.5 mg)
Hydrostatic Pressure Modulating Agent . (B)	Crospovi-done XL-10 (8 mg)	Crospovi-done XL-10 or INF-10 (6.4 mg)	Crospovi-done XL-10 or INF-10 (3.60 mg)	Crospovi-done XL-10 or INF-10 (3.60 mg)	Crospovi-done XL-10 or INF-10 (3.60 mg)	Crospovi-done XL-10 (1.54 mg)	Crospovi-done XL-10 (1.2 mg)
Active Agent (C)	Caffeine (70 mg)	Theophyl-line (80 mg)	Nifedipine (60 mg)	Diltiazem (60 mg)	Buspirone HCl (20 mg)	Ranitidine HCl (60 mg)	Tramadol HCl (200 mg)
A/B	35:1	50:1	50:1	47.5:1	47.5:1	132:1	167:1
A/C	4:1	4:1	3:1	2.8:1	8.6:1	3.4:1	1:1

Acrylic-acid polymers cross-linked with allylsucrose or allylpentaerythritol are sold under the trademark Carbopol®. The specification so-states, for example, on page 17, lines 7-12. Cross-linked polyvinylpyrrolidone is sold under the trademark Polyplasdone® Crospovidone XL-10 or INF-10. The specification so-states, for example, on page 19, lines 15-20. Claim 1 also is amended to further define the recited hydrodynamic fluid-imbibing polymer and the hydrostatic pressure modulating agent based on the definitions provided in claims 14 and 18 and at page 6, lines 1-12 of the description. Claims 12 and 14 are amended to delete recited group **iv**. Claims 12, 14, 15, 17-20 and 34-35 are amended to correct dependencies.

Independent claims 37-41 are added. Claims 37-41 are based on original claims 17, 22, 23, 25 and 30, respectively. The Examiner indicated in the Office Action, dated July 16, 2003 (page 6), that claims 17, 22, 23, 25 and 30 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. New claims 37-41 correspond to original claims 17, 22, 23, 25 and 30, respectively, rewritten in independent form. No new matter is added.

REJECTIONS OF CLAIMS 1, 3-8, 10-32 and 34-36 UNDER 35 U.S.C. § 103(a) OVER FRITSCH *et al.* (US 5,213,794)

Claims 1, 3-8, 10-12, 14-32 and 34-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,213,794 (Fritsch *et al.*) because Frisch *et al.* allegedly teaches a tablet formulation that includes all elements recited in the claims, but fails to teach the recited ratios. The Examiner urges that optimization of ratios is an obvious design choice. Applicant respectfully traverses Examiner's rejections of claims 1, 3-8, 10-11, 14-32 and 35 for the reasons set forth below. As applied to claim 36, the rejection has been rendered moot by the cancellation of claim 36 herein. Applicant respectfully submits that the rejection as applied to claims 12 and 34 has been rendered moot by the amendment of those claims to depend from new claim 40 instead of claim 1.

RELEVANT LAW

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.,* 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the

prior art suggests the desirability of the modification. *In re Fritch,* 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh,* 315 F.2d 381, 137 U.S.P.Q.43 (CCPA 1963).

In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti,* 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach, 212* USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller,* 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination *(ACS Hosp. Systems, Inc. v Montefiore Hosp.,* 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.,* 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 1 is directed to a hydrostatic delivery system that includes a hydrostatic couple and an agent of interest, where the hydrostatic couple includes one, or more than one hydrodynamic fluid-imbibing polymer comprising one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol, and one, or more than one hydrostatic pressure-modulating agent comprising one, or more than one crosslinked polyvinylpyrrolidone, and where the agent of interest is released at a rate that is substantially concentration independent. Furthermore, the weight ratio of the one, or more than one hydrodynamic fluid-imbibing polymer to the one, or more than one hydrostatic pressure modulating agent is from about 35:1 to about 167:1, and the weight ratio of the one, or more than one hydrodynamic fluid-imbibing polymer to the agent of interest is from about 1:1 to about 9:1. Claims 3-8, 10-11, 14-32 and 35 depend from claim 1 and are directed to various embodiments thereof.

TEACHINGS OF FRITSCH *et al.* (US 5,213,794)

Fritsch *et al.* teaches a composition that includes an antacid, calcium polycarbophil (a calcium salt of polyacrylic acid crosslinked with divinyl glycol) and crospovidone (cross-linked polyvinylpyrrolidone; see Example 1, column 6, lines 19-54). The compositions according to Fritsch *et al.* may be administered as chew tablets (see Column 5 line 33), or they are characterized by dissolving rapidly (see Column 5 lines 27-34 and Column 6 lines 50-54), and liberate granule particles that adhere to the gastric mucosa (e.g. Col 5 lines 10-16; Col 6 lines 52-53). The weight ratio of calcium polycarbophil to crospovidone used in Example 1 is about 3:1 (1,000 mg/343 mg), and the weight ratio of calcium polycarbophil to hydrotalcite is 1:1 (1,000 mg/1,000 mg).

Differences Between the Claimed Subject Matter and the Teaching of Fritsch *et al.*

The instantly claimed hydrostatic delivery system produces a steady-state efflux, or a controlled release of the agent of interest over a period of time (see page 23, lines 9-24; Figures 2-6) at a rate that is substantially concentration independent (see for example page 26, lines 29-31). Applicant respectfully submits that Fritsch *et al.* does not teach or suggest a composition that includes an active ingredient in combination with one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol (hydrodynamic fluid-imbibing polymer) and one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone (hydrostatic pressure modulating agent) as in instant claim 1, wherein the weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to the one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone is from about 35:1 to about 167:1, and where the weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to said agent of interest is from about 1:1 to about 9:1, and where the agent of interest is released at a rate that is substantially concentration independent.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

As noted, to establish a *prima facie* case of obviousness, the cited art must teach the desirability of the modification (*In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992)). In this instance, the cited art fails to teach or suggest "the desirability of the modification" of its teachings to result in the instantly claimed system. There is no suggestion in Fritsch *et al.* to modify its formulation to arrive at the system as claimed herein.

The system of instant claim 1 requires a weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol (hydrodynamic fluid-imbibing polymer) to the one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone (hydrostatic pressure modulating agent) is from about 35:1 to about 167:1, and the weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to the agent of interest is from about 1:1 to about 9:1 and that the agent of interest is released at a rate that is substantially concentration independent. Fritsch *et al.* does not teach or suggest a composition that includes an active ingredient in combination with one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol and one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone as in instant claim 1, wherein the weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to the one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone is from about 35:1 to about 167:1, and wherein the weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to said agent of interest is from about 1:1 to about 9:1. Applicant respectfully submits that the recited weight ratios of the components of the presently claimed system result in a *controlled* rate of release of the active ingredient that is substantially concentration independent, regardless of the nature of the active agent. Fritsch *et al.* does not teach or suggest a system that provides a controlled rate of release of an active ingredient that is substantially concentration independent, regardless of the nature of the active agent.

The ordinarily skilled artisan would not have known from the teachings of Fritsch *et al.* or the general art whether or how to adapt the composition of Fritsch *et al.* in order to result in a controlled rate of release of the active ingredient that is substantially concentration independent, regardless of the nature of the active agent. The reference does not teach a composition that results in a substantially concentration independent controlled rate of release of an active ingredient, nor does the cited reference teach or suggest which of its polymers to combine or in what weight ratio to combine them in order to influence the rate of release of the agent from the system. Thus, there is no suggestion in Fritsch *et al.* to do that which Applicant has done.

Also, Fritsch *et al.* provides no motivation for modifying its rapidly disintegrating delivery system so that the rapid dispersion of active ingredient is replaced with a controlled

rate of release of the active ingredient that is substantially concentration independent, nor suggests any desirability of such a modification.

In addition, the proposed modification of the composition of Fritsch *et al.* to result in a controlled rate of release of the active ingredient that is substantially concentration independent would change the principle of operation of the composition of Fritsch *et al.* The "delivery system" of Fritsch *et al.* is designed to easily disintegrate on contact with an aqueous medium so that the agglomerates containing the antacid or active agent can quickly be dispersed so that they can freely distribute and adhere to the gastric mucosa. It is pointed out that the weight ratios of the components used in Fritch *et al.*, e.g., in Example 1 of Fritsch *et al.*, do **not** result in a controlled release of the particles of the hydrotalcite active agent, but rather results in a rapid dispersion of these particles (Column 6, lines 50-54). Thus, modifying the weight ratios of the components used in Fritch *et al.* to do what Applicant has done to achieve a controlled release rate of active ingredient that is substantially concentration independent would change the principle of operation of the Fritch *et al.* composition, which rapidly disperses drug particles from the composition so that they can freely distribute to the gastric mucosa.

Therefore, because (a) there is no suggestion in Fritsch *et al.* to modify its formulation to arrive at the system as claimed herein, (b) Fritsch *et al.* provides no motivation for modifying its rapidly disintegrating delivery system so that the rapid dispersion of active ingredient is replaced with a controlled rate of release of the active ingredient that is substantially concentration independent, nor suggests any desirability of such a modification, and (c) the proposed modification of the composition of Fritsch *et al.* to do what Applicant has done would change the principle of operation of the prior art invention being modified, it is respectfully submitted that the teachings of the reference are not sufficient to render the claims *prima facie* obvious. The Examiner has not shown that the cited reference teaches or suggests to a person of ordinary skill in the art to make the changes that would produce the claimed subject matter, nor that such modifications would result in all of the elements of the claimed subject matter. Applicant respectfully requests that the rejection under 35 U.S.C. 103(a) against claims 1, 3-8, 10-32 and 34-36 be reconsidered and withdrawn.

REJECTIONS OF CLAIMS 1, 3-8, 10-32 and 34-36 UNDER 35 U.S.C. § 103(a) OVER RORK *et al.* (US 5,582,838)

Claims 1, 3-8, 10-12, 14-32 and 34-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,582,838 (Rork *et al.*) because Rork *et al.* allegedly teaches compositions with the same ingredients but fails to teach the recited ratios. The

Examiner urges that the particular ratios represent an obvious design choice. Applicant respectfully traverses Examiner's rejections of claims 1, 3-8, 10-11, 14-32 and 35 for the reasons set forth below. As applied to claim 36, the rejection has been rendered moot by the cancellation of claim 36 herein. The Examiner's rejection of claims 12 and 34 has been rendered moot by the amendment of those claims to depend from new claim 40 instead of claim 1. Applicant respectfully traverses Examiner's rejections of claims 1, 3-8, 10-11, 14-32 and 35 for the reasons set forth below.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above.

TEACHINGS OF RORK *ET AL.* (US 5,582,838)

Rork *et al.* teaches a device that includes an inner core of two layers, one containing a beneficial agent and a polymer that forms microscopic beads when hydrated, and a water insoluble impermeable polymeric coating applied to the core (col. 3, lines 30-43). Rork *et al.* teaches a composition that includes nifedipine, Carbopol 974P (a carboxypolymethylene of acrylic acid crosslinked with allyl ethers of sucrose or pentaerythritol), and Povidone K-90 (polyvinylpyrrolidone; see Example 2, column 13, lines 18-59), which is used as an excipient. Rork *et al.* teaches that the release rate of the active agent is controlled by the number, size and configuration of the apertures cut in the insoluble coating of the core (col. 11, lines 31-36).

Differences Between the Claimed Subject Matter and the Teachings of Rork *et al.*

Rork *et al.* does not teach or suggest a delivery system that includes an agent of interest, one, or more than one hydrodynamic fluid-imbibing polymers including acrylic acid polymer cross-linked with allylsucrose or allylpentaerythritol; and one, or more than one hydrostatic pressure-modulating agent including cross-linked polyvinylpyrrolidone, wherein the weight ratio of the one, or more than one hydrodynamic fluid-imbibing polymer to the one, or more than one hydrostatic pressure modulating agent is from about 35:1 to about 167:1, and wherein the weight ratio of the one, or more than one hydrodynamic fluid-imbibing polymer to said agent of interest is from about 1:1 to about 9:1 and where the agent of interest is released at a rate that is substantially concentration independent. Rork *et al.* does not teach or suggest cross-linked polyvinylpyrrolidone as an ingredient.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

As noted, to establish a *prima facie* case of obviousness, the cited art must teach the desirability of the modification (*In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992)). In this instance, the cited art fails to teach or suggest "the desirability of the modification" of its teachings to result in the instantly claimed system. There is no suggestion in Rork *et al.* to modify its formulation to arrive at the system as claimed herein.

The system of instant claim 1 requires a weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to the one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone is from about 35:1 to about 167:1, and the weight ratio of the one, or more than one hydrodynamic fluid-imbibing polymer to the agent of interest is from about 1:1 to about 9:1 and where the agent of interest is released at a rate that is substantially concentration independent. Rork *et al.* does not teach or suggest a composition that includes an active ingredient in combination with one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol (hydrodynamic fluid-imbibing polymer) and one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone (hydrostatic pressure modulating agent) as in instant claim 1, wherein the weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to the one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone agent is from about 35:1 to about 167:1, and wherein the weight ratio of the one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol to said agent of interest is from about 1:1 to about 9:1. Applicant respectfully submits that the recited weight ratios of the components of the presently claimed system result in a *controlled* rate of release of the active ingredient that is substantially concentration independent, regardless of the nature of the active agent.

Rork *et al.* teaches that the rate of release of a beneficial agent from its composition is determined by the selection of the size and number of apertures through its water-impermeable coating, which subsequently expose the surface of the core to the environment (col. 11, lines 52-55). There is no teaching or suggestion that a controlled release of an agent of interest can be achieved by eliminating the water impermeable coating of Rork *et al.*, nor is there any guidance for selecting a combination of ingredients that when combined in a drug delivery system will release an agent of interest at a rate that is substantially concentration

independent. The ordinarily skilled artisan would not have known from the teachings of Rork *et al.* or the general art whether or how to adapt the composition of Rork *et al.* in order to result in a controlled rate of release of the active ingredient that is substantially concentration independent, regardless of the nature of the active agent. The cited reference does not teach or suggest which of its polymers could be combined or in what weight ratio they could be combined in order to influence the rate of release of the drug from its system if its water-impermeable coating were replaced with a combination of polymers to control drug release rate. Thus, there is no suggestion in the Rork *et al.* to do that which the instant applicant has done. Also, Rork *et al.* does not teach or suggest any desirability of such a modification and provides no motivation for modifying its delivery system.

Further, Rork *et al.* does not teach or suggest cross-linked polyvinylpyrrolidone as an ingredient. Instead, Rork *et al.* teaches using polyvinylpyrrolidone as a stabilizing agent or to aid in the production of tablets, and suggests that polyvinylpyrrolidone is equivalent to a long list of ingredients in this functionality, such as lactose, magnesium stearate, microcrystalline cellulose, starch, stearic acid, calcium phosphate, glycerol monostearate, sucrose, gelatin, methylcellulose, sodium carboxymethyl-cellulose, sorbitol, mannitol and polyethylene glycol. Rork *et al.* does not teach or suggest or provide any motivation for substituting a cross-linked polyvinylpyrrolidone for any ingredient in its formulation, nor suggest any desirability of such a modification or substitution.

In addition, the proposed modification of the composition of Rork *et al.* so that it controls the rate of release of the active ingredient by replacing its insoluble coating that surrounds the core with a combination of one, or more than one acrylic-acid polymer cross-linked with allylsucrose or allylpentaerythritol and one, or more than one homopolymer of a cross-linked polyvinylpyrrolidone as in instant claim 1 would change the principle of operation of the composition of Rork *et al.* Rork *et al.* teaches a delivery device that delivers a beneficial agent by erosion, and that the rate of delivery of its beneficial agent is controlled by the rate of erosion of the layers surrounding the core of its device that contains the beneficial agent. Rork *et al.* teaches that exposing its device to an aqueous environment results in hydration of the microscopic bead forming polymer at the surface of the core of the tablet. The polymer beads then erode from the surface, resulting in the beneficial agent being delivered into the environment at nearly a zero order delivery rate. Rork *et al.* teaches controlling the rate at which the bead forming polymer is hydrated by controlling the number, size and configuration of the apertures cut in the insoluble coating exposing the core. Thus, the device of Rork *et al.*

is complete onto itself. In light of the teachings of Rork *et al.*, a skilled artisan would modify the drug delivery rate by adjusting the size, number and location of the holes in the water-insoluble barrier, thereby increasing or decreasing the hydration of the polymers therein. There is no suggestion or motivation for replacing the rate-modifying insoluble coating of Rork *et al.* with a combination of hydrodynamic fluid-imbibing polymer and hydrostatic pressure modulating agent in a weight ratio of the hydrodynamic fluid-imbibing polymer to the hydrostatic pressure modulating agent of from about 35:1 to about 167:1, and the weight ratio of the hydrodynamic fluid-imbibing polymer to the agent of interest of from about 1:1 to about 9:1 to control of the rate of erosion Rork *et al.*'s drug-containing microscopic beads. Further, changing the hydrostatic conditions within the device of Rork *et al.* would effect the hydration of the polymers and exudation of the hydrated polymers from the Rork *et al.* device. Thus, modifying the weight ratios of the components used in Rork *et al.* to do what Applicant has done to achieve a controlled rate of release of the active ingredient that is substantially concentration independent would change the principle of operation of the Rork *et al.* composition.

Therefore, because (a) there is no suggestion in Rork *et al.* to modify its formulation to arrive at the system as claimed herein, (b) Rork *et al.* does not teach or suggest cross-linked polyvinylpyrrolidone and provides no motivation for substituting a cross-linked polyvinylpyrrolidone for any ingredient in its formulation, (c) Rork *et al.* provides no motivation for modifying its delivery system so that the delivery of active ingredient by erosion of microscopic drug-containing beads is replaced with a controlled rate of release of the active ingredient that is substantially concentration independent, nor suggests any desirability of such a modification, and (d) the proposed modification of the system of Rork *et al.* to do what Applicant has done would change the principle of operation of the prior art invention being modified, it is respectfully submitted that the teachings of the reference are not sufficient to render the claims *prima facie* obvious. The Examiner has not shown that the cited reference teaches or suggests to a person of ordinary skill in the art to make the changes that would produce the claimed subject matter, nor that such modifications would result in all of the elements of the claimed subject matter. Applicant respectfully requests that the rejection under 35 U.S.C. 103(a) against claims 1, 3-8, 10-32 and 34-36 be reconsidered and withdrawn.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,

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